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10/523,466	10/13/2005	Etienne Pays	VANM290.002APC	3679

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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
03/18/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/523,466	PAYS ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *4-7, 13-20 and 22-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8-12 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I in the reply filed on 2/5/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 4-7, 13-20 and 22-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-3, 8-12 and 21 (apolipoprotein L-1 and fragments thereof and methods of treatment/prevention using said *protein/fragments* only) are currently under examination.

Claim Objections

2. Claims 1 and 11 are objected to because of the following informalities: they contain non-elected subject matter which must be removed from the claim, e.g., polynucleotide, cell and inhibitor. Appropriate correction is required.

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 11 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim reads on a product of nature because it does not state that the protein has been isolated.

Claim Rejections - 35 USC § 112-2nd paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 8-12 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, 11 and 12 are vague and indefinite because they are drawn to a protein which is identified solely by name, e.g., apolipoprotein L-1. The mere recitation of a name to describe the invention is not sufficient to satisfy the Statute's requirement of adequately describing and setting forth the inventive concept. The claim should provide any structural properties, such as the amino acid sequence of the protein or molecular weight and source, which would allow for one to identify the protein without ambiguity. The mere recitation of a name does not adequately define the claimed protein.

Claim 1 is vague and indefinite because it is unclear what is encompassed by 'an *adequate* pharmaceutical carrier or diluent". How does one determine adequacy? The metes and bounds of this language cannot be understood. Additionally, as stated above, the non-elected 'elements' must be removed from the claim. Appropriate correction is required.

Claim 2 is vague and indefinite because it is unclear what is meant by the protein 'corresponding to SEQ ID NO: 1". How does the protein 'correspond'? It is unclear whether the protein consists or comprises the sequence set forth in SEQ ID NO:1 or if there are just some other similarities. Applicants should amend this language for clarity.

Additionally, it is unclear what is encompassed by the phrase "an homologue polypeptide". Additionally, the 'an' should be changed to 'a'. How is the polypeptide 'homologous'? This term can read on a polypeptide having just a few amino acids in common. Appropriate correction is requested.

Claims 1 and 3 are vague and indefinite due to the phrase 'pharmaceutically active fragment'. What is the pharmaceutical activity that is being referenced? Pharmaceutical activity encompasses a huge amount of completely different activities and therefore it is unclear what the metes and bounds of this phrase encompass. Without an understanding of the pharmaceutical activity which is being referenced it is not possible to determine which structure is being claimed. While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed.

Claim 12 is vague and indefinite because it is unclear what is encompassed by the phrase "an homologue polypeptide". How is the polypeptide 'homologous'? This term can read on a polypeptide having just a few amino acids in common. Additionally, the 'an' should be changed to 'a'. Appropriate correction is requested.

Claim Rejections - 35 USC § 112-Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3, 8-12 and 21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "an isolated polypeptide comprising SEQ ID NO: 1 (and the specific fragments recited in claim 3)", **does not** reasonably provide enablement for pharmaceutical compositions comprising *any* apolipoprotein L-1, or to an apolipoprotein L-1 corresponding to *any* homolog polypeptide of SEQ ID NO:1 or for any method of *prevention or treatment* of diseases induced in mammals caused by *any* species of Trypanosmoma through the administration of the polypeptide comprising SEQ ID NO: 1 or the generic 'apolipoprotein L-1 or homologs' to said mammals. Diagnostic kits comprising any apolipoprotein L-1 or any size fragment thereof are also not enabled. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant claims are drawn to pharmaceutical compositions comprising *any* apolipoprotein L-1, or to an apolipoprotein L-1 corresponding to *any* homolog polypeptide of SEQ ID NO:1. The claims are also drawn to method of *prevention or treatment* of diseases induced in mammals caused by *any* species of Trypanosmoma through the administration to said mammals. Diagnostic kits comprising any apolipoprotein L-1 or any size fragment thereof are also claimed.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

First, the breadth of the instant claims is drawn to polypeptides which are not specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions.

The instant claims are drawn to proteins comprising a sequence with any given percent similarity to a protein, e.g., homolog. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple

antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native, and be ineffective in treating or preventing diseases or conditions or for detection. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different nucleotide substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a dingle amino acid difference may account for markedly different biological activities. The prior art also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the significance of the particular amino acids and sequences for different amino acids cannot be predicted *a priori*, but must be determined from case to case by painstaking experimental study.

The specification is also not enabled for pharmaceuticals, vaccines or methods of using the full-length proteins set forth in SEQ ID Nos: 1, variants or homologs of these polypeptides to protect or treat any disease by any species of Trypanosoma, or the fragmetns recited in claims 9, 10 and 21. The instant specification provides neither *in*

vitro or *in vivo* results of treating or protecting against diseases caused by these organisms. In such an unpredictable art, specific evidences would need to be present in order to enable such a scope of invention. The specification is not enabled for use of variant polypeptide sequences or fragments or homologs in any of the claimed treatment methods or as a diagnostic. The location of protective epitopes have not been identified. Often times it takes more than one epitope to provide a protective effect. As stated above, selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. The prior art (see Tytler et al Mol. and Biochem. Parasitolog. 69 (1995): 9-17, specifically page 16) has taught that chemotherapy has been the standard treatment of African trypanosomes because they evade the immune system of the mammalian hosts by changing their variant surface glycoproteins which make up the surface coat of the bloodstream forms. Accordingly, the use of treatment other than chemotherapeutic agents, such as protein, has been highly unpredictable. It would take undue experimentation for one of skill in the art to use any of the claimed fragments, homologs or even the full-length polypeptide to *prevent,* much less treat, disease caused by any trypanosomes. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in

return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112-Written Description

8. Claims 1-3, 8-12 and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:1 and therefore the written description is not commensurate in scope with the claims drawn to any homolog.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for

purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Reiger et al (Glossary of Genetics and Cytogenetics, Classical and Molecular, 4th Ed., Springer-Verlay, Berlin, 1976) clearly define alleles as one of two or more alternative forms of a gene occupying the same locus on a particular chromosome..... and differing from other alleles of that locus at one or more mutational sites (page 17). Thus, the structure of naturally occurring allelic sequences are not defined. With the exception of SEQ ID NO:1, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved

by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

No disclosure, beyond the mere mention of allelic variants is made in the specification. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore, the full breadth of the claims does not meet the written description provisions of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3, 11 and 12 rejected under 35 U.S.C. 102(b) as being anticipated by Duchateau et al (J.Lipid Research. 42: 62—630. 2001).

Duchateau et al disclose a protein called apolipoprotein L (apoL). The protein is described as a 'human' protein. The terms "pharmaceutical" and "diagnostic kit" are intended uses only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to

patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "pharmaceutical carrier" or "diluent" reads on water and therefore would be inherent in the preparation/isolation of the proteins. Claims 1 and 2 doe not require a specific amino acid sequence, e.g., claim 2 allows for homologs and claim 1 only recites the protein by name which is the same as that taught by Duchateau. Further, although Duchateau do not specifically recite that their human apolipoprotein comprises SEQ ID NO: 1, absent evidence to the contrary, it inherently would given it is from the same source, possesses the identical function and name. The mere discovery of the amino acid sequence to an already known polypeptide does not impart novelty. Since the Patent Office does not have the facilities for examining and comparing applicants' product with the product of the prior art reference, the burden is on applicants to show an unobvious distinction between the material structural and functional characteristics of the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USP PQ 430 (CCPA 1977).

11. Claims 1-3, 11 and 12 rejected under 35 U.S.C. 102(b) as being anticipated by Tytler et al (Molec. And Biochem. Parasitology. 1995. pages 9-17)).

Tytler et al disclose a protein called apolipoprotein L (apoL). The protein is described as a 'human' protein. Tytler disclose that the protein is responsible for the cytoxicity of human serum to *Trypanosoma brucei brucei.* The reference teaches that apo L-1 is plays a role in lysis of *Trypanosoma brucei brucei* . Tytler et recite there is potential of exploiting the natural non-immune killing factor as an alternative

chemotherapy for African trypanosmiasis. The terms "pharmaceutical" and "diagnostic kit" are intended uses only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "pharmaceutical carrier" or "diluent" reads on water and therefore would be inherent in the preparation/isolation of the proteins. Claims 1 and 2 doe not require a specific amino acid sequence, e.g., claim 2 allows for homologs and claim 1 only recites the protein by name. Further, although Tytler et al do not specifically recite that their human apolipoprotein comprises SEQ ID NO: 1, absent evidence to the contrary, it inherently would given that it is from the same source, possesses the identical function and name. The mere discovery of the amino acid sequence to an already known polypeptide does not impart novelty. Since the Patent Office does not have the facilities for examining and comparing applicants' product with the product of the prior art reference, the burden is on applicants to show an unobvious distinction between the material structural and functional characteristics of the claimed product and the product of the prior art. See In re Best, 562 F.2d 1252, 195 USP PQ 430 (CCPA 1977).

12. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 7:30 AM-6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Shanon Foley, can be reached on (571) 272-0898.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645